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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,781	08/15/2001	George Y. Wu	A32407-PCT-USA-A 065125.0	2538

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,781	WU ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1002, 0303*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed September 22, 2003 has been entered. The application is now in compliance with the Sequence Rules.

Claims 1-5 are pending in the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 2 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of U.S. Patent No. 6,525,242 in view of U.S. Patent Application No. 2001/0007153. Although the conflicting claims are not identical, they are not patentable distinct from each other because one of skill in the art would recognize that the non-human mammal of Claim 1 of the patent could readily be infected with Hepatitis C virus, given that the mammal comprises human hepatocytes, particularly in view of the teachings of U.S. Patent Application No. 2001/0007153.

Claim 1 of the instant application is directed to a model system for Hepatitis C virus infection in humans, comprising a non-human animal rendered immunologically tolerant to human hepatocytes and subsequently transplanted with human hepatocytes and infected with Hepatitis C virus.

Claims 3-5 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 of U.S. Patent No. 6,525,242 in view of U.S. Patent Application No. 2001/0007153. Given the teachings of U.S. Patent Application No. 2001/0007153 (further discussed herein below), the invention of Claims 3-5 would have been *prima facie* obvious.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application No. 2001/0007153 A1 (filed June 16, 1997; Brown et al.).

Brown et al. discloses a non-human animal model having incorporated therein a solid chimeric organ in a manner such that the animal, previously incapable of supporting a viral or pathogenic infection, becomes susceptible to infection. The reference teaches that it is particularly desirable to make animals that support a Hepatitis C infection (see paragraph 0038). The reference specifically teaches that, in the absence of stimulation, intrasplenic injection of hepatocytes can create a chimeric liver with approximately 1% of the hepatocytes derived from an allogeneic or xenogeneic donor (paragraph 0039).

The reference further teaches that a higher representation of donor cells may be achieved by administration of compounds that are hepatotoxic, such as D-galactosamine, carbon tetrachloride, and pyrrolizidine alkaloids (paragraph 0039). The reference teaches inducing immunotolerance by specific suppression of an immune reaction (paragraphs 0043 and 0044). The reference specifically points out that the same allogeneic or xenogeneic source used for the implantation can be used as a source for the tolerization as well and that, although intact hepatocytes are needed for the implantation, lysates of cells have been found to be as effective as whole cells for induction of tolerance (paragraph 0044). The reference specifically teaches using the HuH-7 cell line (paragraph 0092)

Thus, the claimed invention is disclosed in the prior art.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,034,297 (Vierling).

Claim 1 is directed to a model system for Hepatitis C virus infection in humans, comprising a non-human animal rendered immunologically tolerant to human hepatocytes and subsequently transplanted with human hepatocytes an infected with Hepatitis C virus.

Although the specification states that the term "tolerant" does not refer to a state of general immunosuppression, but rather indicates a state of antigen-induced non-responsiveness of lymphocytes achieved by clonal deletion, cell-mediated suppression, or anergy directed specifically toward the introduced human cells (page 18, paragraph 0062 of specification), one of skill in the art would understand the term "tolerant" to encompass general immunosuppression. The more narrow interpretation suggested in the specification is not the conventional understanding in the art. Furthermore, the claims do not require specific immunosuppression. Thus, the term tolerant is construed to broadly encompass general immunosuppression as well as specific immunosuppression.

Vierling discloses that immunocompromised hosts comprising functional human hepatocytes support Hepatitis C virus infection and replication *in vivo*. The immunocompromised hosts are scid/scid mice. See especially Claim 1.

Thus, the claimed invention is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rhim et al. (1995) in view of U.S. Patent No. 6,034,297 (Vierling).

Claim 1 is directed to a model system for Hepatitis C virus infection in humans, comprising a non-human animal rendered immunologically tolerant to human hepatocytes and subsequently transplanted with human hepatocytes an infected with Hepatitis C virus.

Although the specification states that the term "tolerant" does not refer to a state of general immunosuppression, but rather indicates a state of antigen-induced non-responsiveness of lymphocytes

achieved by clonal deletion, cell-mediated suppression, or anergy directed specifically toward the introduced human cells (page 18, paragraph 0062 of specification), one of skill in the art would understand the term "tolerant" to encompass general immunosuppression. The more narrow interpretation suggested in the specification is not the conventional understanding in the art. Furthermore, the claims do not require specific immunosuppression. Thus, the term tolerant is construed to broadly encompass general immunosuppression as well as specific immunosuppression.

Rhim et al. disclose the introduction of rat liver cells into the livers of immunotolerant albumin-urokinase (Alb-uPA) transgenic mice. The reference further discloses that up to 100% of hepatocellular gene expression was of rat origin. The reference points out that immunotolerant Alb-uPA transgenic mice can be made to comprise human hepatocytes within the liver as well. At page 4946, the reference states that "the demonstration that Alb-uPA mouse livers can be reconstituted with rat hepatocytes raises the exciting possibility that they also can be reconstituted with human liver cells. These human-mouse livers could potentially be used as a repository for human hepatocytes, as reagents for human carcinogenicity studies, or as models for human liver disease." The reference does not explicitly mention infecting the human-mouse livers with Hepatitis C.

Vierling discloses that immunocompromised hosts comprising functional human hepatocytes support Hepatitis C virus infection and replication *in vivo*. The immunocompromised hosts are scid/scid mice. See especially Claim 1.

Since the prior art discloses that it was desirable to prepare a small animal model comprising human hepatocytes for studying Hepatitis C virus (HCV) infection, one of skill in the art would have been motivated to implant human hepatocytes (either infected with HCV or free of HCV) into the Alb-uPA transgenic mice disclosed by Rhim et al. to provide an animal model for HCV infection. The skilled artisan would have had a reasonable expectation of success for establishing an Alb-uPA transgenic mouse comprising viable human hepatocytes because Vierling had already successfully produced other

immunocompromised mice comprising viable human hepatocytes and was further able to infect the human hepatocytes with HCV *in vivo*.

One of skill in the art would have been motivated to combine the teachings of Rhim et al. and Vierling to obtain the advantage of producing an *in vivo* liver that is nearly 100% of human origin as was achieved when Rhim et al. implanted rat cells in the Alb-uPA transgenic mice.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/39810 (Knudsen, 1996) in view of U.S. Patent No. 6,034,297 (Vierling).

Claim 1 is directed to a model system for Hepatitis C virus infection in humans, comprising a non-human animal rendered immunologically tolerant to human hepatocytes and subsequently transplanted with human hepatocytes an infected with Hepatitis C virus.

Although the specification states that the term "tolerant" does not refer to a state of general immunosuppression, but rather indicates a state of antigen-induced non-responsiveness of lymphocytes achieved by clonal deletion, cell-mediated suppression, or anergy directed specifically toward the introduced human cells (page 18, paragraph 0062 of specification), one of skill in the art would understand the term "tolerant" to encompass general immunosuppression. The more narrow interpretation suggested in the specification is not the conventional understanding in the art. Furthermore, the claims do not require specific immunosuppression. Thus, the term tolerant is construed to broadly encompass general immunosuppression as well as specific immunosuppression.

Knudsen discloses immunocompromised hosts comprising functional human hepatocytes. The reference further discloses that the animals are useful for studying hepatitis viruses. The reference does not specifically mention HCV.

Vierling discloses that it was desirable to have a small animal model for HCV infection. See especially Claim 1.

Since the prior art discloses that it was desirable to prepare a small animal model comprising human hepatocytes for studying Hepatitis C virus (HCV) infection, one of skill in the art would have been motivated to infect the animals described by Knudsen with HCV for the purpose of studying HCV infection *in vivo*. The skilled artisan would have anticipated a reasonable expectation of success because Vierling had already successfully infected immunocompromised mice comprising viable human hepatocytes with HCV.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (703) 305-3482.

Art Unit 1632 will be moving to the new USPTO headquarters on January 13, 2004. After that date, Examiner Falk can be reached at (571) 272-0728 and Examiner Reynolds can be reached at (571) 272-0734.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER